pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review
Final Economic Guidance Report

Pertuzumab (Perjeta) for Metastatic Breast Cancer

December 3, 2013

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1 ECONOMIC GUIDANCE IN BRIEF

1.1 Background

The main economic analysis **submitted to pCODR by Hoffman-La Roche Ltd** compared pertuzumab and trastuzumab combination therapy (Perjeta-Herceptin Combo Pack) with docetaxel to standard first-line therapy of trastuzumab and docetaxel for patients with HER2+ locally recurrent, unresectable or metastatic breast cancer (MBC). Pertuzumab, trastuzumab and docetaxel are administered intravenously.

According to the pCODR Clinical Guidance Panel (CGP), this comparison is appropriate. The current standard of care for first-line MBC includes trastuzumab combined with a taxane, which can include docetaxel or paclitaxel. Trastuzumab can also be used with vinorelbine in patients who cannot receive a taxane. It is possible that similar outcomes would be observed with other chemotherapies. However, the submitted economic model is based only on clinical evidence with docetaxel chemotherapy and should not be generalized to other chemotherapies without clinical input or new data verifying that the outcomes would be similar.

Patient Advocacy Group Input considered the following factors important in the review of pertuzumab, which are relevant to the economic analysis: The factors most important to patients are access to treatments that could delay progression and extend life expectancy. Patients also felt it important to have manageable side effect profiles and maintain quality of life and lifestyle, but would be willing to accept toxicities for survival benefit.

A full summary of the patient advocacy group input is provided in the pCODR Clinical Guidance Report.

The **Provincial Advisory Group (PAG)** considered that the following factors would be important to consider if implementing a funding recommendation for pertuzumab, and which are relevant to the economic analysis:

- same patient population and treatment and monitoring protocols as trastuzumab apply to pertuzumab; therefore implementation resources will be minimal.
- the availability of individual pertuzumab vials instead of within the combo pack;
- the potential for use of pertuzumab and trastuzumab with other chemotherapies (other taxanes or vinorelbine).

At the confidential price pertuzumab and trastuzumab (Perjeta-Herceptin Combo Pack) costs $[redacted] and includes one 420mg vial of pertuzumab and one 440mg vial of trastuzumab. *(Non-disclosable economic information was used in this pCODR Guidance Report and the manufacturer requested this information not be disclosed pursuant to the pCODR Disclosure Guidelines. This information will remain redacted until notification by manufacturer that it can be publicly disclosed)* Pertuzumab is administered as a fixed dose of 420mg, thus the full vial is consumed. The loading dose is doubled to 840mg pertuzumab and 8mg/kg trastuzumab. At the list price the pertuzumab (Perjeta-Herceptin Combo Pack) costs $6,448. At the recommended dose of 420 mg pertuzumab and 6mg/kg trastuzumab every 3 weeks, the average cost per day is $301 and the average cost per 28-day course is $8,417. For the recommended loading dose of 840mg pertuzumab and 8mg/kg trastuzumab, the average cost per day is $465 and the average cost per 28-day course for the first month is $13 031.

Trastuzumab is available as 440 mg/vial at a cost of $2,700 per vial. At the recommended dose of 6mg/kg every 3 weeks, the average cost per day is $123 and the average cost per 28-day course is $3434. For the recommended loading dose of 8mg/kg, the average cost

per day is $153 and the average cost per 28-day course for the first month is $4292. These costs are based on the assumption of no wastage of trastuzumab.

1.2 Summary of Results

The EGP's best estimate of the incremental cost-effectiveness ratio (ΔC / ΔE) is between $262,263 / QALY gained and $303,726 / QALY gained when the addition of pertuzumab is compared with trastuzumab and docetaxel. The results are affected by the assumptions about carry over post-progression survival benefit as well as the duration beyond the trial period that pertuzumab could continue to reduce risk of progression and death.

The incremental cost-effectiveness ratio is based on an estimate of the extra cost (ΔC) and the extra clinical effect (ΔE).

- The extra cost (ΔC) of pertuzumab is between $100,699 and $117,932. Costs included the drug acquisition costs, chemotherapy administration costs, treatment of adverse events, and supporting and subsequent treatment costs.
- The extra clinical effect (ΔQALY or ΔLY) of pertuzumab is between 0.332 and 0.450 QALYs. Key clinical effects considered in the analysis included progression-free and post-progression survival gains and small improvement in quality-of-life for pertuzumab compared to trastuzumab and docetaxel alone in the progression-free state.

The EGP based these estimates on the model submitted by Roche and reanalyses conducted by the EGP. The submitted model was based on CLEOPATRA, a phase III RCT in which combination of pertuzumab, trastuzumab and docetaxel was compared with placebo, trastuzumab and docetaxel among patients with HER2+ MBC who have not received prior anti-HER2 therapy or chemotherapy for metastatic disease. Patients in the model were followed for 10 years, which the Clinical Guidance Panel believed to be a reasonable time horizon.

In the submitted model, it was assumed there was a carry-over benefit from pertuzumab in post-progression survival. However, there is no direct support for post-progression survival gain from pertuzumab in the clinical trial data. (See section 2.2.3, pages 16-18 for more details). There does not appear to be any statistical reasons to believe that there is any carry-over effect beyond progression based on trial data. The manufacturer suggested carry-over benefit should be considered in the "lower bound" ICER estimate. Based on the data in the model, the post-progression survival curves observed from the trial are closely intertwined and cross each other at several points. The CGP reviewed these curves and agreed that there is no current evidence to support the possibility of a carry-over benefit with pertuzumab. The post-progression survival curves used by the manufacturer model to extrapolate to a 10 year horizon are separated and the area between the two curves represents the survival benefit the manufacturer assumed in its model beyond progression. The EGP does not believe the difference in the modeled PPS curves is justified based on the observed overlapping trial post-progression survival curves. Therefore the EGP considered it most appropriate to exclude any carry-over benefits in the model, and reanalyzed the model with equal risk of death from progressed disease in both treatment groups.

- The lower estimate ($262,263 / QALY gained) is based on equal post-progression survival (equal risk of death from progressed disease) between treatment groups.

The extra cost (ΔC) of pertuzumab is $117,932 and the extra clinical effect (ΔE) of pertuzumab is 0.450 QALYs.

In the submitted model, it was also assumed that pertuzumab would continue to reduce risks of progression and death indefinitely, based on extrapolation of the survival curves from the clinical trial. As the clinical benefit may attenuate over time, particularly after discontinuation of treatment, this may be an optimistic assumption. The EGP removed the risk reduction from pertuzumab beyond the trial duration (37 months). In other words, after the trial, patients in each group had equal risks of both progression and death (and the model was still run for 10 years).

- The upper estimate ($303,726 /QALY gained) is based on convergence of the PFS survival curves beyond the clinical trial period (37 months). This is a conservative scenario of equal progression and death beyond the trial data, and represents the upper bound of cost-effectiveness estimates. The purpose of the "upper bound" of the ICER estimate is provide an idea where we think the true ICER is not likely to be beyond. The EGP believes that it is unlikely that the true ICER will be beyond this "upper bound". The extra cost (ΔC) of pertuzumab in this scenario is $100,699 and the extra clinical effect (ΔE) of pertuzumab is 0.332 QALYs.

The EGPs estimates differed from the submitted estimates. According to the economic analysis that was submitted by Roche, when the addition of pertuzumab is compared with trastuzumab and docetaxel:

- the extra cost (ΔC) of pertuzumab is $120,287. Costs considered in the analysis included the drug acquisition costs, chemotherapy administration costs, treatment of adverse events, and supporting and subsequent treatment costs.
- the extra clinical effect (ΔE) of pertuzumab is 0.505 quality-adjusted life years gained or 0.642 life years gained (LYG) (7.7 months). The clinical effect considered in the analysis was based on progression-free and post-progression survival gains and small improvement in quality-of-life for pertuzumab compared to trastuzumab and docetaxel alone in the progression-free state.

So, the Submitter estimated that the incremental cost-effectiveness ratio (ΔC / ΔE) was $238,014 / QALY gained and the incremental cost per LYG was $187,376. The Submitter's sensitivity analysis results ranged from $141,000 to $263,000 for the cost/QALY.

1.3 Summary of Economic Guidance Panel Evaluation

If the EGP estimates of ΔC, ΔE and the ICER differ from the Submitter's, what are the key reasons?

The EGP estimates differ from the Submitter's due to the removal of post-progression survival gain and assumptions about the reduction in risk of progression with pertuzumab beyond the trial duration. The current clinical trial data do not show any evidence of post-progression carry-over benefits, and thus, the EGP used the same post-progression survival estimates for both treatment groups. The manufacturer further suggested that we could consider pooling the two PPS curves. As individual patient data are not available, the EGP was not able to perform pooling of the two PPS curves. Based on EGP's re-analysis, using either of the two PPS curves for both treatment arms results in ICERs that differ by less than $1,000/QALY gained. Therefore the EGP believes that pooling the PPS data may not substantially change our "lower bound" ICER estimates. As a result, the EGP continues to

believe that the current "lower bound" of $262,263/QALY provides a useful guide for the "lower bound" for the ICER range.

The EGP also formulated a conservative upper bound of cost-effectiveness where the progression-free survival curves converge immediately after the trial period. The EGP believes that it is unlikely that the true ICER will be beyond this "upper bound". Therefore, the EGP continues to believe that the current upper bound of $303,726/QALY provides a useful guide for the upper bound for the ICER range.

Were factors that are important to patients adequately addressed in the submitted economic analysis?

Yes. The factors relevant to patients included improvement in efficacy outcomes and quality of life, which are reflected in the model. The model includes a difference in quality of life between progression free and progressed disease states, and the effects on treatment on response and the effects of six grade 3/4 (febrile neutropenia, diarrhoea and vomiting , hand-foot syndrome, stomatitis, fatigue, hair loss) treatment-related toxicities. Any treatment-related toxicities that were not included in the quality of life measures were likely to have a very small impact on the results.

Is the design and structure of the submitted economic model adequate for summarizing the evidence and answering the relevant question?

Yes. The submitted model was well designed and reasonable inputs were used. The model structure used is similar to that of others for metastatic breast cancer and captures the relevant health states. The model uses phase III RCT data for clinical inputs and the structure permits reanalysis of the assumptions for extrapolating beyond the trial data by the EGP.

For key variables in the economic model, what assumptions were made by the Submitter in their analysis that have an important effect on the results?

The variables that have the largest impact on the results were the assumptions of carry-over post-progression survival benefit, and the duration beyond the clinical trial of reduced risk for progression or death that would be expected from treatment with pertuzumab. The reduction in risk persisting for the full model duration may be optimistic given that most patients had discontinued treatment at the latest data cut-off (median follow-up of 30 months). If the beneficial effects of pertuzumab are not maintained indefinitely beyond the trial, the ICER increases. The EGP reanalysis made more reasonable and conservative assumptions for each of these parameters. Other assumptions made by the Submitter did not substantially affect the results of the analysis.

Were the estimates of clinical effect and costs that were used in the submitted economic model similar to the ones that the EGP would have chosen and were they adequate for answering the relevant question?

Yes. The clinical data were based on the pivotal CLEOPATRA clinical trial for pertuzumab in combination with trastuzumab and docetaxel, including the clinical data, the drug dosing and administration, and the rates of adverse events. The EGP would consider

different quality of life estimates based on the published literature for this parameter, and this was considered in reanalysis. The EGP also would not assume a carry-over survival benefit for pertuzumab after progression and discontinuation of treatment, and would not assume that the clinical benefits in reducing progression and death would persist several years beyond the clinical trial duration; both of these assumptions were modified in the reanalysis. As of the latest data cut-off, 74% of pertuzumab patients and 83% of comparator patients had withdrawn from treatment as a result of progressive disease, toxicity or other reasons (Swain et al 2013). Thus, patients may not continue to experience the same level of benefit, particularly after discontinuation of therapy. Despite requests from the EGP, the Submitter could not provide evidence to statistically support a carry-over effect, nor has a biological mechanism been identified. As such, including a carry-over effect overestimated the clinical benefit.

1.4 Summary of Budget Impact Analysis Assessment

What factors most strongly influence the budget impact analysis estimates?

The budget impact was most sensitive to the drug acquisition price for the pertuzumab and trastuzumab combo pack, uptake rates and treatment durations expected with each therapy. Both trastuzumab and pertuzumab are used until progression or unacceptable toxicity; the BIA uses the median PFS from the CLEOPATRA trial (18.5 months pertuzumab and trastuzumab vs. 12.4 months trastuzumab) to estimate average treatment duration.

The model was not sensitive to choice of chemotherapy backbone (docetaxel, paclitaxel, vinorelbine), since these drugs have similar costs, are much less expensive treatments and are only used for a fixed duration (6 cycles).

What are the key limitations in the submitted budget impact analysis?

The budget impact analysis does not consider any growth in patient numbers over time, which should be validated using clinical input. The general rate of cancer incidence is growing over time in Canada.

1.5 Future Research

What are ways in which the submitted economic evaluation could be improved?

The submitted economic model would be improved with further statistical analysis of the post-progression period to assess and appropriately handle carry-over effects and statistical analysis of the rates of adverse events to inform the model.

Is there economic research that could be conducted in the future that would provide valuable information related to the addition of pertuzumab for first-line metastatic breast cancer?

Specific quality of life data for these patients suitable for use in a model could be collected or derived from the health-related quality of life assessment conducted alongside the clinical trial to better inform the quality of life estimates used in the model.

Additionally, of use would be clinical data of pertuzumab and trastuzumab with other taxanes.

2 DETAILED TECHNICAL REPORT

This section outlines the technical details of the pCODR Economic Guidance Panel's evaluation of the economic evidence that is summarized in Section 1. Pursuant to the *pCODR Disclosure of Information Guidelines*, this section is not eligible for disclosure. It was provided to the pCODR Expert Review Committee (pERC) for their deliberations.

3 ABOUT THIS DOCUMENT

This Economic Guidance Report was prepared by the pCODR Economic Guidance Panel and supported by the pCODR Breast Clinical Guidance Panel and the pCODR Methods Team. This document is intended to advise the pCODR Expert Review Committee (pERC) regarding resource implications and the cost-effectiveness of pertuzumab (Perjeta) for metastatic breast cancer. A full assessment of the clinical evidence of pertuzumab (Perjeta) for metastatic breast cancer is beyond the scope of this report and is addressed by the relevant pCODR Clinical Guidance Report. Details of the pCODR review process can be found on the pCODR website (www.pcodr.ca).

pCODR considers it essential that pERC recommendations be based on information that can be publicly disclosed. Information included in the Economic Guidance Report was handled in accordance with the *pCODR Disclosure of Information Guidelines*. The manufacturer, as the primary data owner, did not agree to the disclosure of some economic information, therefore, this information was redacted from this publicly available Guidance Report.

This Final Economic Guidance Report is publicly posted at the same time that a pERC Final Recommendation is issued. The Final Economic Guidance Report supersedes the Initial Economic Guidance Report.

The Economic Guidance Panel is comprised of economists selected from a pool of panel members established by the pCODR Secretariat. The panel members were selected by the pCODR secretariat, as outlined in the pCODR Nomination/Application Information Package and the Economic Guidance Panel Terms of Reference, which are available on the pCODR website (www.pcodr.ca). Final selection of the pool of Economic Guidance Panel members was made by the pERC Chair in consultation with the pCODR Executive Director. The Economic Guidance Panel is editorially independent of the provincial and territorial Ministries of Health and the provincial cancer agencies.

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